

# Dairy Sessions

Moderator: Walter Guterbock, Edwin Kreykes

## Vaccination of Dairy Cattle

**Victor Cortese, DVM, PhD, Diplomat ABVP (dairy)**

Director Cattle Immunology, Pfizer Animal Health, 746 Veechdale Road, Simpsonville, KY 40067, Victor.Cortese@pfizer.com

### Abstract

Studies continue to design the best vaccination programs for today's dairy herds and to maximize immune function. Designing a vaccination program involves a good history of the individual farm as well as a basic understanding of the immune system. The vaccines chosen should have good solid efficacy studies (as well as effectiveness and efficiency studies if possible) to ensure that the product can fulfill the needs of the farm or ranch. Management decisions may be made that do not maximize the potential of the product chosen and realistic expectations of all products should be well explained to the producer before they are used. The owner should be involved in the vaccine decision making process and all of the information on the product should be shared.

The establishment of good baseline immunity in replacement heifers is the foundation of the vaccination program and can have dramatic effects on the health and profitability of the herd and needs to be well planned.

### Résumé

Par leurs études, les chercheurs continuent d'améliorer les programmes de vaccination des troupeaux laitiers de façon à maximiser leurs fonctions immunitaires. L'élaboration d'un programme de vaccination nécessite de bien connaître l'historique sanitaire de la ferme et de comprendre les principes de base du système immunitaire. Pour s'assurer que le vaccin réponde aux besoins de la ferme ou du ranch, on vérifiera si des études ont confirmé son efficacité potentielle (ainsi que son efficacité réelle et son efficacité, si possible). Il arrive que le producteur prenne des décisions de gestion qui ne tirent pas profit de tout le potentiel d'un produit. D'autre part, on doit l'informer de ce à quoi il peut réalistement s'attendre de chacun des produits avant qu'il ne les utilise. Également, le propriétaire doit s'impliquer dans la décision concernant le vaccin et toute l'information sur le produit doit lui être communiquée.

L'implantation d'une bonne immunité de base chez les génisses de remplacement est le fondement

du programme de vaccination. Elle peut avoir un effet spectaculaire sur la santé et la rentabilité du troupeau, d'où l'importance de bien la planifier.

### Introduction

In order to scientifically choose a vaccine or design a particular vaccination program for today's dairies it is necessary to consider many variables.<sup>32</sup> The increased movement and purchasing of cattle seen with today's larger herds puts additional stress on the vaccine program as disease risk rises. Thus, vaccine programs need to be science based more than ever before. When designing a vaccination program, a good history is needed before the program can be built. This should include:

1. Presence and degree of challenge of particular diseases on the dairy.
2. Management practices on the facility that lend themselves to or hinder the implementation of vaccination programs.
3. At what times or ages the disease problems are occurring, and whether they are associated with any stresses.
4. What is the status of the herd? Is it open or closed? Are they purchasing animals and at what age? Are the calves home-raised or grown by others? What age are they returning?
5. What is the breeding program? Are clean-up bulls used? Source of the bulls and age of the bulls at purchase?

Some basic questions also need to be asked about specific vaccines being considered for inclusion in the vaccination program:

1. What immune system components are necessary to afford protection against the various diseases?
2. Some basic immunology concepts.
3. The information that is available on products being considered, and the source and quality of the information.
4. Label indications for duration of immunity and maternal antibody interference.

5. Warnings or restrictions on the use of the particular vaccine.
6. If used in calves, have maternal antibody studies been performed with the specific vaccine being considered for use?

### Challenge

The level of disease challenge and degree of protection are in a continual state of fluctuation on a dairy and in a particular animal. The level of protection is different in every vaccinated animal due to biological variability and day to day stresses the animal may be undergoing. The same is true with the amount of exposure to a pathogen. Overwhelming challenge can override the immunity and lead to disease even in well-vaccinated animals, as shown in Figure 1.

### Timing of Disease

Many farms will have consistent times when certain diseases occur. The timing may give some insight into stresses that are occurring in the management of the cattle. Correcting these stresses can have a positive impact on vaccination and lessen disease susceptibility. Furthermore, this type of a history is helpful to determine the timing of vaccinations. This is a concept that is often under utilized in veterinary medicine. Knowing when a problem has historically occurred will allow vaccinations to be scheduled when they will give maximum immune responses in preparation for anticipated challenges. As a general rule, vaccines should precede the anticipated problem by at least two weeks. With the development of newer, fast acting vaccines, this may become an even more important method of controlling diseases.

## Immunology of Dairy Cattle

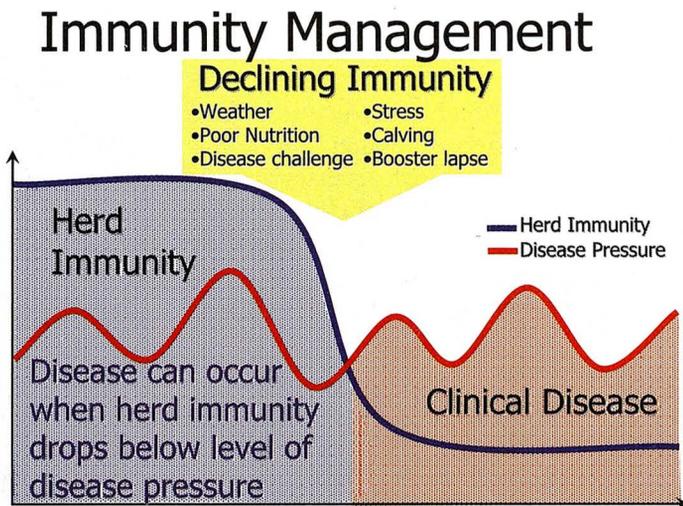
### Development of the Prenatal Immune System

The immune system of all species of mammals begins development fairly early in gestation. As the fetus grows, the immune system goes through many changes as cells appear and become specialized. In general, the shorter the gestation period, the less developed the immune system is at birth.<sup>28</sup> However, the fetus does become immunocompetent to many diseases while in utero. In calves, this has been demonstrated with a wide variety of diseases.<sup>11,23,43,47</sup> For these types of diseases, pre-colostrum titers from the neonate can be used for diagnostic determination of fetal exposures. The primordial thymus can be seen in both fetal lambs and calves between days 27 to 30 as an epithelial chord.<sup>2,37</sup> As a percentage of body weight, the thymus reaches its maximum size near mid-gestation, then rapidly decreases after birth. Actual regression of the thymus begins around puberty, and the extent and speed in which it regresses will vary by husbandry practices and genetics. By the time of first heat cycle, the thymus' function as an immune gland is almost completely gone.

The cells that initially infiltrate the thymus are of unknown origin, but thymic development and differentiation of thymocytes into specific CD cell lines occurs during gestation. Some of this development and differentiation can occur in secondary lymphoid organs as well. B cells, by contrast, develop and differentiate in the fetal bone marrow. There is a steady increase in the peripheral lymphocytes throughout gestation.<sup>64</sup> The majority of these circulating fetal lymphocytes are T cells. At the same time that lymphocytes are developing in the fetus, development and expansion of other white blood cell populations is occurring.

### The Neonatal Immune System

The systemic immune system is fully developed, albeit immature, in the neonate at the time of birth. However, the local immune system goes through rapid development after birth. Susceptibility of the newborn to pathogens is not due to any inherent inability to mount an immune response, but is due to the fact that their immune system is unprimed<sup>65</sup> and the local immune system is underdeveloped. Although there are higher numbers of phagocytic cells in the neonate, the function of these cells is decreased (in calves, these deficiencies are found up to four months of age).<sup>29</sup> Complement is from 12-60% of adult levels at birth, and will not reach adult levels in calves until they are six months of age. There is a slow maturation of the immune system in mammals. As an animal approaches sexual maturity and begins to cycle, the immune system also matures. In cattle, most of the immune system maturity is seen by five to eight months of age. For example, T cells (CD4+, CD8+ and



**Figure 1.** Various stresses or overwhelming exposure to infectious agents can lead clinical disease

TCR $\gamma\delta$ + cells) do not reach peak levels until the animal is eight months of age.<sup>30</sup> This does not mean a young calf cannot respond to antigens but the response will be weaker, slower, and easier to overcome. For all practical purposes, this immaturity may lead to moderation of disease rather than the complete prevention. Since the placenta is of the epitheliochorial type in food animal species (cattle, pigs, sheep), there is no transplacental transfer of antibodies or white blood cells. Therefore, no discussion on bovine neonatal immunology is complete without a discussion of an important component of the newborn calf's defense mechanism...colostrum.

### *Colostrum*

Colostrum is the most important example of passive immunity. Defined as the "first" secretion from the mammary gland present after birth, colostrum has many known and unknown properties and components. The information on both the short and long term impacts of colostrum in calves continues to grow. Not only does good passive transfer impact morbidity and mortality in the young calf,<sup>6,55,56</sup> but it also has a positive impact on long term health and production.<sup>16,24,71</sup> Constituents of colostrum include concentrated levels of antibodies and many of the immune cells (B cells, CD cells, macrophages, and neutrophils), which are fully functional after absorption by the calf.<sup>53</sup> Additional components of the immune system, such as interferon, are transferred via colostrum,<sup>34</sup> along with many important nutrients.<sup>62</sup> The primary colostral antibody in most domestic species is immunoglobulin (Ig) class G, which in ruminants is further defined as IgG1. The function of the various cells found in colostrum is still undergoing much research. The cells are known to enhance defense mechanisms in the newborn animal in the following ways: transfer of cell-mediated immunity; enhanced passive transfer of immunoglobulins, which stimulate development of neonatal antigen presenting cells; local bactericidal and phagocytic activity in the digestive tract; and increased lymphocyte activity.<sup>19,34,50</sup> Recent research has demonstrated that only cells that have been exposed to the colostral environment are absorbed and traffic into the neonatal bloodstream. These cells also demonstrate different homing patterns. Finally, calves deprived of maternal colostral leukocytes up-regulate receptors associated with physiological stress.<sup>59</sup>

These cells are destroyed by freezing and naturally disappear from the calf between three to five weeks of age.<sup>20</sup> The long term impacts of these cells on health and/or production of calves is not well understood at this time.

### *Vaccination to Improve Colostral Quality*

It has long been thought that vaccines administered to a cow before calving will increase colostral antibodies against specific antigens. This has been best

demonstrated with vaccines against neonatal diarrhea pathogens that are administered to cows. These vaccines are designed to increase the colostral antibody concentration against specific organisms that cause diarrhea in calves such as *Escherichia coli*, *rotavirus*, and *coronavirus*.<sup>44,59,60</sup> However, little research has been done looking at other vaccines and their impact on colostral antibodies. While one study demonstrated that vaccinating cows with a modified-live viral vaccine increased colostral antibodies,<sup>20</sup> a recent study with inactivated viral vaccination of cows did not show the same response.<sup>46</sup> One Israeli study actually demonstrated decreased colostral antibodies when cows were vaccinated before calving.<sup>8</sup> If a vaccine is being incorporated into a program primarily to improve colostral transfer of antibodies, then studies should be requested that demonstrate the vaccine's ability to produce the desired effect.

### *Maternal Antibody Interference Revisited*

One of the commonly held beliefs in neonatal immunology is that the presence of maternal antibody will block the immune responses associated with vaccination. This has been based on vaccinating animals followed by evaluating subsequent levels of antibody titers. It is clear from many studies that if animals are vaccinated in the presence of high levels of maternal antibody to that antigen, they may not display increased antibody titers following vaccination.<sup>7,41</sup> However, recent studies have shown both the formation of B cell memory responses<sup>39,48,49</sup> as well as cell-mediated immune responses in the face of maternal antibody<sup>46</sup> when attenuated vaccines were used. Similar responses have been reported in laboratory animals as well.<sup>26,35,52,61</sup> It is clear from these studies that maternal antibody interference of vaccines is not as absolute as once thought. The immune status of the animal, particularly against that antigen, the specific antigen, and its presentation should be considered when trying to design vaccination programs when maternal antibody may be present. Recent work has indicated the ability to stimulate an immune response in the face of maternal antibody may even be vaccine specific.<sup>21,67</sup> In summary, work published to date has demonstrated that vaccination against diseases which have a primary cell-mediated protective mechanism may be more likely to stimulate an immune response in the face of maternal antibody than those of which humoral immunity is the primary protective mechanism, as shown in Table 1.

### *Impact of Stress*

Stress impacts the calf's immune system as it does in older animals. There are several factors that can affect the immune system that are unique to the neonatal animal. The calving process has a dramatic impact on the newborn's immune system due to corticosteroid release. Furthermore the newborn has an increased

**Table 1.** Diseases with research that has assessed maternal antibody interference in cattle.

Primarily cell-mediated protection – vaccination not blocked by maternal antibody	Primary antibody protection – vaccination blocked by maternal antibody
BRSV	Bovine viral diarrhea
BHV-1	<i>Mannheimia haemolytica</i>
Parainfluenza virus	<i>Pasteurella multocida</i>
<i>Leptospira borgpetersenii</i>	
Pseudorabies	

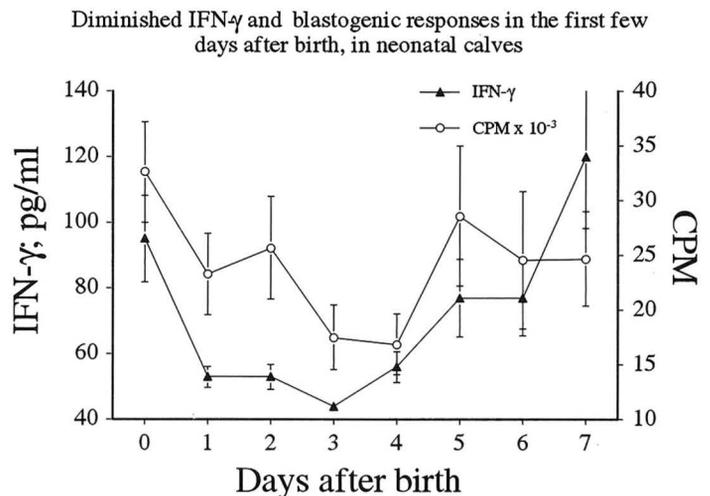
number of suppressor T cells. These factors along with others dramatically decrease systemic immune responses for the first week of life. Recent research has demonstrated that there is actually a decrease in the immune response of neonatal calves. Figure 2 shows that after birth, there is a decrease in immune responses until day 3 when they are at their lowest levels (Rajaraman *et al*, 1997). By day 5 these responses are back to the level of immune responses seen on the day of birth. Systemically administered vaccinations during this time should be avoided due to these decreased responses. Vaccination immediately after birth may even have undesired effects.<sup>9</sup> Furthermore, other stresses should be avoided in the young calf to try and maintain immune system integrity in the immunologically frail newborn. Procedures such as castration, dehorning, weaning, and movement need to be considered as stresses that have the potential to decrease immune system function temporarily.

The impact of stress on older cattle has been extensively studied.<sup>3,4,10,69,70</sup> Decreased immune function can be measured beginning four weeks prior to calving, and does not rebound to normal levels until five weeks post-calving. These decreased immune responses include delayed inflammation by reducing efficiency of immune surveillance by neutrophils, decreased phagocytic cell function, increased trafficking of  $\delta\gamma$  T cells into epithelial sites, decreased IFN- $\gamma$  secretion by lymphocytes, decreases antibody production by B-cells, and decreased  $T_{H1}$  responses. This immune suppression may also delay or impair response to vaccines: therefore, post-parturient or post-stress vaccination should be delayed until reasonable immune responses can be expected.

### Choosing Vaccines

#### Assessing Vaccine Efficacy

Vaccine efficacy can be extremely difficult for the practitioner to assess. Traditionally, serologic data showing pre- and post-vaccination titers has been equated to protection. For many diseases there is a poor correlation



**Figure 2.** This graph illustrates the immune dysfunction present in the neonatal calf and shows diminished cytokine (IFN $\gamma$ ) production and blastogenic (CPM is counts per minute) responses in the first few days after birth. Graph courtesy of Dr. Marcus Kehrli, National Animal Disease Center.

between an antibody being measured and the protection generated by the vaccine in the animal, and a recent study showed an inverse relationship between antibody levels and protection against bovine viral diarrhea virus (BVDV).<sup>38,57</sup> Recently, cell-mediated immune function tests have been added to show a more complete stimulation of the immune response after vaccination.<sup>1</sup> Although this gives more information on the vaccine, it still does not answer the basic question of how well a vaccine really protects. This can only be answered by well-designed challenge studies. In order to assess a challenge study, the following information is needed:

1. Trial design, including animal characteristics
2. Statistical analysis of the results
3. Route of administration of the challenge
4. Characteristics of the challenge organism
5. Method for clinical score assignment
6. Publication of the results in a peer-reviewed article
7. Impact of the challenge on the control group.

Unfortunately, for many of our diseases, the challenge model is not well established.

Field trials are even harder to assess, but are valuable at answering the effectiveness (i.e. the efficacy in a particular situation) and efficiency of vaccines (cost effectiveness of a vaccine).<sup>45</sup> There are several good references on field trial analysis available.<sup>40,52</sup>

The best place to begin the analysis of a vaccine is with the label and accompanying insert. The USDA grants one of five different levels of protection based on the data submitted for vaccine licensing.<sup>12,66</sup> The inserts will also list any duration of immunity studies and warn-

ing and precautions. Familiarity with the labels and a periodic review of all vaccines that are recommended in the program are essential for proper vaccination program design.

#### *Modified-live Versus Inactivated Vaccines*

Each company's development and manufacture of cattle vaccines is different, thus the composition of the vaccine will vary dramatically among different manufacturers. Outlines of production are proprietary for each manufacturer, however some information can be found in technical and marketing pieces. For example, some viral vaccines are grown on bovine-derived kidney cell lines, whereas others are grown on porcine-derived kidney cells. Some vaccines are grown on only calf serum and some are grown on both calf and fetal calf serum. Differences in passages may be found as well. The variability is seen in the following areas:

- a. Strain(s) chosen for the vaccine
- b. Number of passages chosen in the growth
- c. Growth medium
- d. Number of viral or bacterial particles in the vaccine particles.

Three basic technologies are available today in cattle viral and bacterial vaccines.<sup>18,28</sup>

1. Modified-live (attenuated) vaccines contain living bacterial or viral organisms. They are usually collected from a field disease and then grown in abnormal host cells (viral) or media (bacterial) to change or attenuate the pathogen. Each time the pathogen is grown through a replication it is called a "passage", and is administered back to the animal to see if it is still virulent. After several passages, the pathogen will begin to lose virulence factors since it cannot cause "disease" in these unnatural host cells. Once the pathogen can no longer cause disease in the target species, it is then tested to see if it can confer protection. The final vaccine is usually passed a number of times beyond the passage where virulence is no longer seen. This decreases the risk of reversion to a virulent pathogen. These vaccines usually require good quality control to decrease the risk of a contaminant entering the vaccine.
2. Inactivated (killed) vaccines are easier to develop since virulence after growth is not a problem. The same pathogen is isolated from a disease outbreak. The pathogen is grown and then chemically or physically killed. The inactivation is usually achieved by either adding a chemical to the pathogen or using ultraviolet rays. The major concern with inactivation is the potential loss of important epitopes. An adjuvant is normally added to inactivated vaccines to heighten

the immune response. The vaccine is then tested for efficacy.

3. Genetically engineered vaccines have been altered genetically, usually through a mutation. This mutation may be induced by several different methods, but the ensuing bacteria or virus has different properties that may alter virulence or growth characteristics. Most of these vaccines are modified-live mutants (temperature-sensitive viral vaccines; streptomycin-dependent *Pasteurellas*) but inactivated marker vaccines are also genetically engineered. These vaccines have been engineered to delete a gene and cause an immune response deficient in antibodies to a certain epitope, allowing diagnostics to differentiate between vaccine and natural exposure responses, such as gene-deleted IBR vaccines.

#### **Designing a Vaccination Program**

Vaccination programs in a cowherd need to be custom designed for the particular needs of the herd. Vaccination programs in the replacement stock have two specific goals that need to be met: the first is to protect the calf against any pathogens that are prevalent in the calves; the second is to prepare the calf for entry into the adult herd with a good foundation of protection from which to build herd immunity. A comprehensive dairy vaccination program should be viewed as a continuum throughout the animal's life as it goes through the different stages of production. The use of many different types of vaccines is routinely done very early in veal, dairy beef, and dairy replacement heifers, particularly where early disease prevention is needed. Effectiveness of these programs is an interaction of several factors, including antigen (i.e. infectious bovine rhinotracheitis vs. *Mannheimia haemolytica*) and vaccine type (i.e. modified-live or inactivated), age of the calf, presence of maternal antibody, other stress factors present at the time of vaccination, and timing of disease agent exposure.

Vaccines that utilize the mucosal immune system have been tested and licensed for use in the young calf, including the newborn. These vaccines include modified-live, intranasal IBR/parainfluenza-3 (PI3) vaccines; modified-live, oral *rotavirus/coronavirus* vaccine; and new intranasal vaccines containing either BVDV types 1 and 2, bovine herpesvirus-1, PI3 and bovine respiratory syncytial virus, or BRSV in combination with PI3 and adenovirus. For BRSV, in which limited replication occurs with systemic modified-live vaccination, intranasal administration may be the most effective route.<sup>22</sup> Exact timing of early vaccination will vary somewhat, depending on antigen and presentation. One study has shown that initial systemic vaccination for the four primary viral diseases (BVDV, IBRV, BRSV, and PI3) has little

impact when administered during the three week to five week of age window in dairy calves.<sup>10</sup> This corresponds to the time frame in which maternal T cells are disappearing from the calf.<sup>16,62</sup> Several other studies have looked at vaccinating calves before three weeks of age with good response.<sup>13,14,21,46,67</sup> In general, vaccination in the young calf should precede anticipated or historical times of disease by at least 10 days, allowing the immune system to respond before exposure. If a booster dose is required, then the booster should be given at least 10 days before the expected disease occurrence. Although in its infancy, the use of vaccination programs in young food animals is gaining popularity and more research is needed to further define protection and the timing required by different vaccines in the neonate.

As discussed above, vaccination programs are tailor made to each dairy. However, there are some basic vaccination recommendations for today's dairy herds. The cornerstone of the herd program is based first on protection against high-prevalence diseases that can have catastrophic impacts on the dairy when infections occur. In North America and many parts of the world, the minimum vaccination program should be built around the four major viral diseases: bovine viral diarrhea virus (types 1 and 2), bovine herpesvirus-1, and bovine respiratory syncytial virus. Many would also include vaccination against the five primary *Leptospira* serovars of cattle due to the potential for high abortion rates, as well as the major clostridial diseases, core endotoxin vaccines, and *Brucella*.

This should be the cornerstone of the program; other pathogens are then optional and are added depending on herd problems or potential risk. At least one five-way modified-live viral vaccine should be included for replacement animals prior to first breeding to establish a strong baseline immunity against BVDV, BRSV, and BHV.<sup>5,15,27,33,68,71</sup> The use of modified-live vaccines in the adult cow has recently received much scrutiny; however, studies have shown a positive impact in vaccinating cows with these vaccines.<sup>17,25</sup> If used during pregnancy it is important to use only products that are labeled to be used during pregnancy and that the labels be followed explicitly.

#### Booster Importance

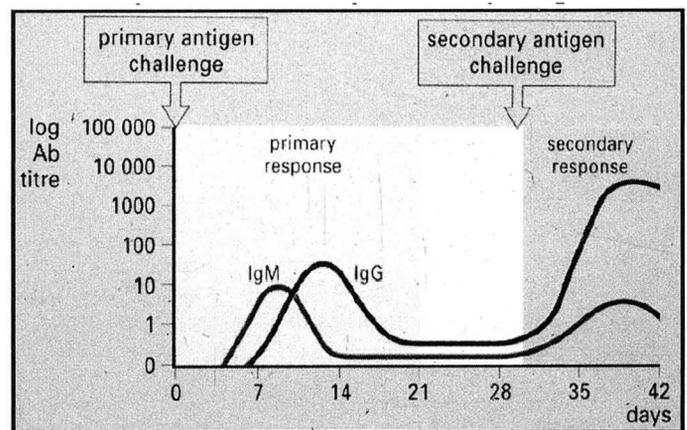
It is important to follow the label directions for administering vaccines. Most inactivated vaccines require a booster before protection is complete. The first time an inactivated vaccine is administered, the primary response occurs. This is fairly short-lived, not very strong, and is predominantly comprised of IgM. The response seen after a booster vaccination is called the secondary or anamnestic response. This is much stronger, of longer duration, and is primarily comprised of IgG.<sup>14,28</sup> T cells follow a similar pattern of an anamnestic response (Fig-

ure 3). If the booster is given too early, the anamnestic response does not occur, and if too much time elapses before the booster is given, it acts as an initial dose and not as a booster. With most modified-live vaccines (with the exception of most BRSV vaccines), the primary vaccination also stimulates the secondary response without needing a booster, since the virus or bacteria is replicating in the animal.

#### Adverse Reactions

Adverse reactions are a potential risk with any vaccination. However, dairy cattle appear to have a higher risk of post-vaccination reactions than other cattle. These reactions fall into three primary types:<sup>28,31,36,39,41,42,48,49,51,54,58,63</sup>

1. IgE and the release of granules from basophils and mast cells mediate immediate hypersensitivity. This reaction is seen within minutes of vaccination, and often begins with shaking or sweating. The majority of these animals will respond to epinephrine.
2. Delayed hypersensitivity is mediated by an antibody-antigen complex attaching to complement and the ensuing activation of the complement cascade. The resultant reaction may occur locally or systemically. The reaction may be delayed as the complexes form and the cascade begins, and subsequent by-products begin to exert their effects. The signs are similar to immediate hypersensitivity and treatment is epinephrine.
3. One of the more common reactions seen in dairy cattle has been associated with the endotoxin and other bacterial components found in most gram-negative vaccines. Currently, there are no requirements for monitoring or reporting the



**Figure 3.** The importance of booster doses when required are shown in this graph. (Roitt I, Brostoff J, Male D: *Immunology*, 4th ed. Mosby Press, Philadelphia, 1998).

amount of endotoxin found in cattle vaccines, and the level of endotoxin may vary dramatically between vaccines and serials of the same vaccine. Furthermore, the potency of endotoxin varies among different gram-negative bacteria. This is seen primarily in Holsteins due to some genetic predisposition, and can be seen following administration of any gram-negative bacterin. The signs seen vary depending on the farm's or individual's sensitivity to gram-negative bacterial components. The number or severity of the gram-negative fractions in the vaccination program administered simultaneously are also instrumental in causing these reactions. As a general rule, no more than two gram-negative vaccines should be administered on the same day to dairy cattle. These adverse reactions include:

- a. anorexia and transient decreases in milk production
- b. early embryonic deaths
- c. abortions
- d. gram-negative bacterial (endotoxic) shock, requiring fluxinin or keprofen, steroids, antihistamines and fluids.

### Conclusions

Designing a vaccination program involves a good history of the individual farm as well as a basic understanding of the immune system. The vaccines chosen should have good solid efficacy studies (as well as effectiveness and efficiency studies if possible) to ensure that the product can fulfill the needs of the farm or ranch. Management decisions may be made that do not maximize the potential of the product chosen, and realistic expectations of all products should be well explained to the producer before they are used. The owner should be involved in the vaccine decision making process, and all of the information on the product should be shared.

The establishment of good baseline immunity of replacement heifers and the foundation vaccination program can have dramatic effects on the health and profitability of the herd, and needs to be well planned.

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